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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,579	06/18/2001	Sujay Singh	IMG-00112.P.1-US	2573

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	8

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/884,579	SINGH ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *1-11,13-15 and 17-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: definition of chimera and transgenic.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group III in Paper No. 7 is acknowledged. The traversal is on the ground(s) that Group II, III and V are patentably distinct but are connected by a transgenic bird having a knockout of an endogenous immunoglobulin gene and an insertion of an exogenous immunoglobulin gene. Therefore, applicants argue the search required for Groups II, III and V would not be undue. This is not found persuasive because the steps of groups III and V are different and would require a different search by the examiner. The burden required to search all the steps encompassed by the methods of isolating antibodies using such birds (Groups III and V) would be undue. The limitations of claims 4, 5 and 7-10 (Group II) require limitations that are not required for Group III. The burden required to search all the limitations of Group II with the steps of Group III would be undue.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 12 requires making a chimeric antibody by immunizing a transgenic avian with an antigen, and isolating a chimeric or exogenous antibody from the serum or an egg of the avian. Claim 16 requires making a xenogeneic antibody by immunizing a transgenic avian with an antigen, and isolating a xenogeneic antibody from the serum or an egg of the avian. Claims 12 and 16 require the transgenic avian has i) an inactivated endogenous heavy chain immunoglobulin gene and ii) an exogenous immunoglobulin gene.

Transgenics are defined as organisms in which new DNA has been introduced into the germ cells by injection into the nucleus of the ovum (Stedman's Medical Dictionary, see attached definition).

The specification suggested inactivating the heavy chain immunoglobulin gene in birds using various methods known in the art, e.g. Jakobovits (US Patent 5,998,209, 12-7-99), Ginsburg (US Patent 6,006,778, 5-23-00) or Kucherlapati (US Patent 5,939,598, 8-17-99) (pg 26, line 15; pg 41, line 15; pg 56, lines 20-25). The references cited and the art at the time of filing taught transfecting mouse ES cells with a knockout construct, culturing the cells over a period of time, selecting the ES cells having the desired knockout and implanting the ES cells into a recipient embryo. See, for example, Kucherlapati who taught selection of mouse ES cells having the desired knockout was required to make a mouse having an immunoglobulin gene knockout (col. 10, line 47). The art at the time of filing did not teach how to inactivate a gene in an avian ES cell or

how to culture a transfected avian ES cell over a period of time such that a transgenic avian was made.

Throughout the specification, the specification suggests introducing the exogenous genes using methods known in the art, both in avians and mice. For example, Stage XI PGCs had been isolated from chickens, transduced with retrovirus, and immediately injected into the vasculature of Stage 15 chick embryos to obtain germline transmission of a transgene (Vick et al., Proc. R. Soc. Lond., 1993, Vol. 251, pg 179-182). Plasmid DNA had been injected into the germinal disc of chick zygotes isolated before being laid to obtain germline transmission of a transgene (Love et al. Bio/Technology, 1994, Vol. 12, pg 60-63). Retroviral vectors had been injected into the subgerminal cavity of an avian embryo in a freshly laid egg to obtain germline transmission of a transgene (Thoroval et al., Transgenic Research, 1995, Vol. 4, pg 369-376). Retroviral vectors had been used to introduce a truncated antibody receptor into chickens "somatically" and express the receptor in the bursa at hatch (Sayegh et al., Dec. 15, 1999, Vol. 72, pg 31-37; pg 32, 2nd full para., lines 2-5 and 16-18; para. bridging pg 33-34). Mohammed (1998, Immunotechnology, Vol. 4, pg 115-125) taught that although using hens for the production of recombinant human antibodies (rhAb) has been discussed, it has never been demonstrated. Mohammed transfected a lymphoblastoid cell line with a retrovirus encoding a rhAb, injected the cells into a chicken and obtained expression of the rhAb in the egg yolk and sometimes the egg white (pg 116, col. 1, 2nd para.; col. 2, 1st full para.). Mohammed suggested suppressing the expression of endogenous chicken Ig but did not teach how to

inactivate a gene in an avian (pg 124, col. 2, para. 2, line 9) and did not teach how to obtain a transgenic avian having an inactivated immunoglobulin gene. Since the time of filing, Isao (2002, Cloning Stem Cells, Vol. 4, pg 91-102) suggested making chickens expressing human antibodies but did not teach how to make transgenic chickens or how to inactivate chicken genes (see abstract).

The specification suggested culturing avian ES cells using the method of Pain after transfection for 10-14 days (pg 59, line 4; Pain, 1996, Development, Vol. 122, pg 2339-2348). However, since the time of filing, Ivarie (Trends in Biotechnology, Jan. 2003, Vol. 21, pg 14-19) taught that because of the complex process by which a bird makes and lays eggs, transgenic procedures for birds have lagged far behind those of other organisms. Ivarie cites Pain who taught long-term culture of non-transfected, blastodermal cells that provided germline transmission; however, no transgenic birds have been made using transfected ES cells or PGCs. The biggest obstacle to overcome in making transgenic birds using transfected ES cells or PGCs is the loss of germline competence during culture of transfected ES cells and PGCs (pg 14, col. 2, 3rd full para., 1st sentence; pg 17, col. 1, 2nd full para., last two sentences; pg 17, sentence bridging col. 1-2; pg 17, col. 2, last sentence).

Thus, the state of the art at the time of filing was that stably transfected avian ES cells and PGCs had not been cultured over a period of time using the method of Pain et al. such that transgenic avians having inactivated genes were obtained.

The specification does not overcome the unpredictability in the art so that one of skill could culture transfected avian ES cells or PGCs and select cells having the

desired knockout and obtain germline chimeras having an inactivated gene as claimed. The specification provides no other means of isolating ES cells or PGCs, transfecting the cells or culturing the transfected cells such that the desired cells could be selected. Without such guidance, it would require one of skill undue experimentation to obtain a transgenic avian having an inactivated gene as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 refers to "the transgenic avian of claim 3" however, claim 3 is drawn to a method of making a transgenic avian. Clarification is required.

Claim 12 is indefinite because the limitation of "exogenous" (also in parent claim 2) is indefinite. It cannot be determined whether the antibody or locus is "exogenous" to all avians, a type of avian, or one particular avian because the term "exogenous" is a relative term.

Claim 12 is indefinite because the limitation of "locus" in parent claims 1-3 is indefinite. The term does not make sense in context of the claim because a "locus" is the position of gene in a chromosome and not a nucleic acid sequence that can be inactivated as claimed.

Claim 12 is indefinite because it is unclear in parent claim 2 if the "exogenous immunoglobulin locus" is introduced into the "at least one cell" of claim 1 or a separate "at least one cell."

Claim 12 is indefinite because parent claim 3 does not clearly set forth the limitation by stating the immunoglobulin is a heavy chain constant region.

Claim 12 is indefinite because it does not clearly set forth the structure of the antibody produced. All antibodies are "chimeric" because they are made up of two chains, i.e. a heavy and light chain. Thus, it is unclear if the antibody isolated is limited to one having the exogenous immunoglobulin or whether any immunoglobulin made up of more than one component are encompassed by the claim. See Stedman's Dictionary definition number 4 of chimera provided. Therefore, the claim does not clearly set forth that the antibody isolated has the exogenous immunoglobulin corresponding to the exogenous immunoglobulin gene introduced into the avian cell.

Claim 16 refers to "the transgenic avian of claim 10" however, claim 10 is drawn to a method of making a transgenic avian. Clarification is required.

Claim 16 is indefinite because the limitation of "xenogeneic" is indefinite. It cannot be determined whether the antibody is "exogenous" to all avians, or a species of avian because the term "xenogeneic" is a relative term.

Claim 16 is indefinite because the limitation of "locus" in parent claims 1, 6, 7 and 10 is indefinite. The term does not make sense in context of the claim because a "locus" is the position of gene in a chromosome and not a nucleic acid sequence that can be inactivated as claimed.

Claim 16 is indefinite because it is unclear in parent claim 6 if the "endogenous immunoglobulin light chain locus" is inactivated in the "at least one cell" of claim 1 or a separate "at least one cell."

Claim 16 is indefinite because it is unclear in parent claim 7 if the "exogenous immunoglobulin light chain locus" is introduced into the "at least one cell" of claim 1 or a separate "at least one cell."

Claim 16 is indefinite because parent claim 10 does not clearly set forth the limitation by stating the immunoglobulin light chain comprises at least a V_L, J_L, and C_L region.

Claim 16 is indefinite because the phrase "the V_L, J_L, and C_L regions" in parent claim 10 lacks antecedent basis.

Claim 16 is indefinite because it unclear whether the exogenous locus in parent claims 7 and 10 is the "xenogeneic" antibody of claim 16 or if the exogenous "locus" combines with an endogenous immunoglobulin to form the xenogeneic antibody.

Claim 16 is indefinite because it does not clearly set forth the structure of the antibody produced. It is unclear if the antibody isolated is limited to one having the exogenous immunoglobulin or encompasses other exogenous immunoglobulins. The claim does not clearly set forth that the "xenogeneic" antibody isolated has the exogenous immunoglobulin corresponding to the exogenous immunoglobulin gene introduced into the avian cell.

Specification

The abstract of the disclosure is objected to because it is too long. Correction is required. See MPEP § 608.01(b).

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER

transgenic (trans-jen'ik)

Referring to an organism in which new DNA has been introduced into the germ cells by injection into the nucleus of the ovum.

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chimera (kī-mēr′ă, kī-)

1. In experimental embryology, the individual produced by grafting an embryonic part of one animal on to the embryo of another, either of the same or of another species.
2. An organism that has received a transplant of genetically and immunologically different tissue, such as bone marrow.
3. Dizygotic twins that retain each other as immunologically distinct types of erythrocytes.
4. A protein fusion in which two different proteins are linked via peptide bonds; usually genetically engineered. Chimeric antibodies may have the Fab fragment from one species fused with the Fc fragment from another.
5. Any macromolecule fusion formed by two or more macromolecules from different species or from different genes.

[L. *Chimaera,* G. *Chimaira,* mythic monster (lit. a she-goat)]

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